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**TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371**

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INTERNATIONAL APPLICATION NO.
PCT/FR99/01372

INTERNATIONAL FILING DATE
10 June 1999

PRIORITY DATE CLAIMED
24 June 1998

**TITLE OF INVENTION: NOVEL FORM OF IRBESARTAN, METHODS FOR OBTAINING SAID FORM AND
PHARMACEUTICAL COMPOSITIONS CONTAINING SAME**

APPLICANT(S) FOR DO/EO/US

FRANC, Bruno, HOFF, Christian, KIANG, San, LINDRUD, Mark, MONNIER, Olivier, WEI, Chenkou

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND or SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1)).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371 (c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An unexecuted oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.

☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
Citation of References

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Filing under 35 U.S.C. § 371
Corresponding to International
Application Serial No.: PCT/FR99/01372

Applicants: FRANC, Bruno, HOFF, Christian,
KIANG, San, LINDRUD, Mark, MONNIER,
Olivier and WEI, Chenkou

International Filing Date: 10 June 1999

For: NOVEL FORM OF IRBESARTAN,
METHODS FOR OBTAINING SAID FORM AND
PHARMACEUTICAL COMPOSITIONS
CONTAINING SAME

Commissioner for Patents
Box PCT
Attn: EO/US
Washington, D.C. 20231

Dear Sir:

PRELIMINARY AMENDMENT

Please amend the above-identified application as follows:

In the Specification:

Please amend the specification as follows:

After the claims, please insert the following abstract as new page 36 (a copy of which is enclosed herewith for the Examiner's convenience):

ABSTRACT

The invention relates to a novel crystalline form of irbesartan, to pharmaceutical compositions containing it, to processes for preparing it, and to a method for treating cardiovascular diseases utilizing it.

In the Claims:

Please amend claims 1-30 and add new claims 31-45 as follows before calculating the filing fee for the above-identified application.

CERTIFICATE UNDER 37 C.F.R. 1.10

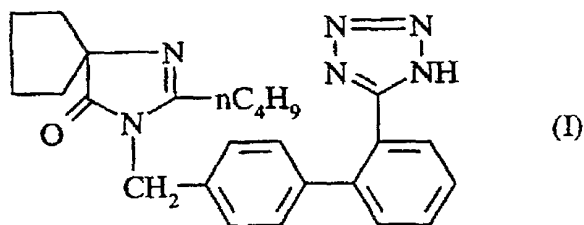
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Date of Deposit: December 19, 2000

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Signature

1. (Amended) A [C]crystalline compound of formula:



having a crystal habit[us] such that the ratio between the length and the width of the crystals is between 1:1 and 10:1.

2. (Amended) A [C]crystalline compound according to Claim 1, in which the ratio between the length and the width of the crystals is between 1:1 and 5:1.

3. (Amended) A [N]novel crystalline form of irbesartan of form A [, characterized in that] wherein the ratio between the length and the width of the crystals is between 1:1 and 5:1.

4. (Amended) A [P]process for preparing a compound according to [any one of Claims 1 to 3, characterized in that] Claim 1 wherein a crystalline suspension of a compound of formula (I) is subjected to at least one sonication episode and at least one temperature oscillation episode.

5. (Amended) A [P]process for preparing a compound to [any one of Claims 1 to 3, characterized in that] Claim 1 wherein a crystalline suspension of irbesartan of acicular habit form A is subjected to at least one sonication episode and at least one temperature oscillation episode.

6. (Amended) A [P]process according to [either of Claims 4 and 5,] Claim 5 in which the temperature oscillation episode comprises a heating phase and a corresponding cooling phase.

7. (Amended) A [P]process according to Claim 6, in which the heating phase precedes the cooling phase.
8. (Amended) A [P]process according to Claim 7, in which the sonication episode is followed by a temperature oscillation episode.
9. (Amended) A [P]process according to Claim 5 [either of Claims 4 and 5,] in which the sonication episode is preceded by a temperature oscillation episode.
10. (Amended) A [P]process according to Claim 5 [either of Claims 4 and 5,] in which the sonication episode is carried out simultaneously with the temperature oscillation episode.
11. (Amended) A [P]process according to Claim 5 [either of Claims 4 and 5,] in which a sonication episode is carried out between 2 temperature oscillation episodes.
12. (Amended) A [P]process according to Claim 5 [either of Claims 4 and 5,] in which the sonication and/or temperature oscillation episodes are repeated independently.
13. (Amended) A [P]process according to Claim 5 [either of Claims 4 and 5,] in which the sonication is carried out in batches, semi-continuously or continuously.
14. (Amended) A [P]process according to Claim 7, in which the heating phase of the temperature oscillation episode is carried out at a temperature of between about 20°C and 100°C.
15. (Amended) A [P]process according to Claim 7, in which the heating phase of the temperature oscillation episode is carried out at a temperature such that about 15% to 25% of the crystals are dissolved in about 60 minutes.

16. (Amended) A [P]process according to Claim 7, in which the cooling phase of the temperature oscillation episode is carried out at a temperature of between about 100°C and -20°C.

17. (Amended) A [P]process according to Claim 7, in which the cooling phase of the temperature oscillation episode is carried out at a temperature of between about -5°C and 20°C.

18. (Amended) A [P]process according to Claim 7, in which the temperature selected for the cooling phase of the temperature oscillation episode is less than the temperature selected for the corresponding heating phase of the temperature oscillation episode.

19. (Amended) A [P]process according to Claim 7, in which the crystalline suspension is seeded with irbesartan crystals whose ratio between the length and the width is between 1:1 and 10:1.

20. (Amended) A [P]process for preparing a compound according to [any one of Claims 1 to 3, characterized in that it contains the steps consisting in] Claim 1 comprising the steps of:

a) preparing a solution of irbesartan acicular habit form A in an alcohol, under concentration and temperature conditions which allow the total solubility of the irbesartan;

b) cooling the said solution to a temperature selected as a function of the concentration of the solution, such that the solution is in the metastable zone;

c) seeding with irbesartan crystals of brick habit;

d) cooling the irbesartan solution to a temperature of between about 20°C and 5°C;

e) subjecting the crystalline suspension thus formed to a mechanical shearing using a shearing machine;

f) heating the crystalline suspension to a temperature of between about 40°C and 60°C to dissolve the fine particles;

g) cooling the crystalline suspension to a temperature of between about 20°C and 5°C;

h) filtering off the crystals of brick habit thus formed.

21. (Amended) A [P]process according to Claim 20, in which, in step a), the irbesartan is dissolved in isopropanol.

22. (Amended) A [P]process according to Claim 20, in which, in step b), a solution containing 50 g/litre to 70 g/litre of irbesartan in isopropanol is cooled to a temperature ranging between 60°C and 80°C.

23. (Amended) A [P]process according to Claim 20, in which, in step c), the solution is seeded with irbesartan crystals whose ratio between the length and the width is between 1:1 and 10:1.

24. (Amended) A [P]process according to Claim 23, in which the seeded solution is maintained at a temperature of between 80°C and 22°C for a few minutes to about 2 hours, before being cooled.

25. (Amended) A [P]process according to Claim 21, in which, in steps b) and d), the rate of cooling is from about 5°C to 20°C per hour.

26. (Amended) A [P]process according to Claim 20, in which, in step e), the mechanical shearing is carried out by a machine having a spin speed of about from 10 000 rpm to 15 000 rpm.

27. (Amended) A [P]process according to Claim 26, in which the mechanical shearing in step e) is carried out either by placing the shearing machine directly in the reactor or by passing the crystalline suspension into the shearing machine.

28. (Amended) A [P]pharmaceutical composition comprising [containing] a compound according to Claim 1 [any one of Claims 1 to 3] and pharmaceutically acceptable excipients.

29. (Amended) A [P]pharmaceutical composition according to Claim 28 further comprising [, containing] a diuretic agent [combined with a compound according to any one of Claims 1 to 3].

30. (Amended) A [P]pharmaceutical composition according to Claim 29, in which the diuretic agent is hydrochlorothiazide.

Please add the following new claims:

31. A process for preparing a compound according to Claim 2 wherein a crystalline suspension of a compound of formula (I) is subjected to at least one sonication episode and at least one temperature oscillation episode.

32. A process for preparing a compound according to Claim 3 wherein a crystalline suspension of a compound of formula (I) is subjected to at least one sonication episode and at least one temperature oscillation episode.

33. A process for preparing a compound according to Claim 2 wherein a crystalline suspension of irbesartan of acicular habit form A is subjected to at least one sonication episode and at least one temperature oscillation episode.

34. A process for preparing a compound according to Claim 3 wherein a crystalline suspension of irbesartan of acicular habit form A is subjected to at least one sonication episode and at least one temperature oscillation episode.

35. A process according to Claim 4 in which the temperature oscillation episode comprises a heating phase and a corresponding cooling phase.

36. A process according to Claim 4 in which the sonication episode is preceded by a temperature oscillation episode.
37. A process according to Claim 4 in which the sonication episode is carried out simultaneously with the temperature oscillation episode.
38. A process according to Claim 4 in which a sonication episode is carried out between 2 temperature oscillation episodes.
39. A process according to Claim 4 in which the sonication and/or temperature oscillation episodes are repeated independently.
40. A process according to Claim 4 in which the sonication is carried out in batches, semi-continuously or continuously.
41. A pharmaceutical composition comprising a compound according to Claim 2 and pharmaceutically acceptable excipients.
42. A pharmaceutical composition comprising a compound according to Claim 3 and pharmaceutically acceptable excipients.
43. A method for the treatment of cardiovascular diseases which comprises administering to a patient in need of such treatment a compound according to Claim 1.
44. A method for the treatment of cardiovascular diseases which comprises administering to a patient in need of such treatment a compound according to Claim 2.
45. A method for the treatment of cardiovascular diseases which comprises administering to a patient in need of such treatment a compound according to Claim 3.

REMARKS

The specification has been amended in order to insert an appropriate Abstract of the invention.

Claims 1-30 have been amended in order to write these claims in the appropriate U.S. claim format.

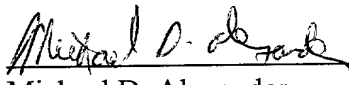
Claims 4-6, 9-13, 20, and 28-29 have also been amended in order to limit the multiple dependencies of these claims.

New claims 31-45 have been added by the foregoing amendments. Support for claims 31-32 occurs, for example, in original claim 4. Support for claims 33-34 occurs, for example, in original claim 5. Support for claims 35-40 occurs, for example, in original claims 6, 9, 10, 11, 12 and 13, respectively. Support for claims 41-42 occurs, for example, in original claim 28. Support for claims 43-45 occurs, for example, on page 1, lines 13-15 of the specification wherein it is stated that the compounds of formula I would be useful in the treatment of cardiovascular diseases.

Claims 1-45 remain in the application.

Respectfully submitted,

Date: December 19, 2000


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ABSTRACT

The invention relates to a novel crystalline form
5 of irbesartan, to pharmaceutical compositions
containing it, to processes for preparing it, and to a
method for treating cardiovascular diseases utilizing
it.

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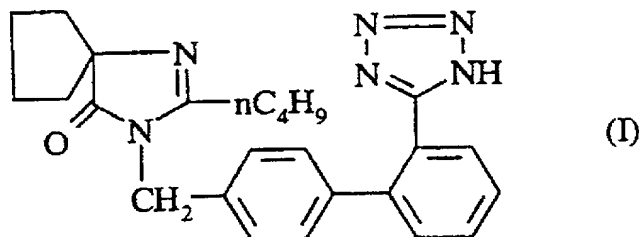
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PCT/FR99/01372

Novel form of irbesartan, processes for obtaining the
said and pharmaceutical compositions containing it

The present invention relates to a novel
5 crystal habit of 2-n-butyl-4-spirocyclopentane-1-[(2'-(
(tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one
of formula:



10

This compound and its method of preparation
were disclosed for the first time in European patent
EP 454 511. The compound of formula (I) is an
angiotensin II antagonist which is useful in the
15 treatment of cardiovascular diseases such as
hypertension, cardiac insufficiency, cardiac
arrhythmia, in the treatment of diseases of the central
nervous system, in the treatment of glaucoma and
diabetic retinopathy and in the treatment of renal
20 insufficiency and diabetic nephropathy.

The common name of the compound of formula
(I) is irbesartan and the term irbesartan is used in
this description and in the claims to refer to the

compounds of formula (I).

European patent application EP 708 103
discloses the existence of 2 crystalline forms of
irbesartan:

- 5 - one, known as form A, is the one obtained
by crystallization in a solvent containing less than
about 10% by volume of water,
- the other, known as form B, is obtained by
crystallization in a water-miscible solvent containing
10 more than about 10% water.

Each of these two forms is characterized by a
specific X-ray diffraction profile.

Patent application EP 708 103 discloses that
form B is a tautomeric form.

- 15 Patent application EP 708 103 indicates that
irbesartan in the form A is in the form of stable, non-
hygroscopic needles of high electrostatic nature.
Hereinbelow in the present description, the term
"acicular habit" denotes this crystalline form of the
20 irbesartan form A.

It also been found that these crystals of
acicular habit are difficult to filter and to dry and
that they display poor flowability.

- 25 A novel crystal habit of the form A has now
been found, characterized in that the ratio between the
length and the width of the crystals is between 1:1 and
10:1, preferably between 1:1 and 5:1. This novel

crystal habit of the form A of irbesartan will be defined by the term "brick habit" of irbesartan hereinbelow in the present description.

A subject of the present invention is also
5 processes for obtaining irbesartan crystals of form A which have the novel crystal habit according to which the ratio between the length and the width of the crystals is between 1:1 and 10:1, preferably between 1:1 and 5:1.

10 The higher this ratio, the longer are the needles relative to their width, and thus an improvement in this ratio means a decrease of the said ratio. It is preferable for this ratio to decrease such that it is between 1:1 and 10:1, preferably between 1:1
15 and 5:1.

The improvement of this ratio means that the crystals have less of a tendency to break or to aggregate when they are wet, they can be filtered and dried faster, and they are easier to handle when they
20 are dry.

The processes according to the invention have no effect on the polymorphism.

The irbesartan crystals in the brick habit have the physicochemical characteristics described
25 below.

The powder X-ray diffraction profile (diffraction angle) was established with a Siemens

D 550 TT diffractometer, and the significant lines are given in Table I below:

Table I

d	I/I ₀
11.22	100.00
7.90	12.02
7.52	13.79
7.23	18.60
6.27	20.14
6.09	6.47
5.86	7.42
5.60	98.76
5.41	19.45
5.05	24.67
4.97	20.36
4.91	12.92
4.80	27.33
4.61	15.90
4.49	14.73
4.36	9.86
4.17	62.84
4.07	15.39
3.97	30.34
3.88	14.32
3.83	13.56
3.75	37.28

3.53	26.48
3.46	12.42
3.40	27.88
3.27	11.03
3.18	10.42
3.15	7.28
3.12	6.11
3.05	15.50
3.01	9.49
2.81	7.11
2.78	9.40

This diffraction profile is that of the form A of irbesartan disclosed in EP 708 103.

The chargeability of the powder is measured by tribogeneration: the powder is subjected to a strong vibration during which it becomes charged on itself, and is then transferred into a Faraday cage connected to a very sensitive electrometer. The chargeability measured varies between 0 and -10 nanocoulomb/g. By way of comparison, the crystals of irbesartan in acicular form A have a chargeability, measured by the same process, of between -30 and -40 nanocoulomb/g.

The packing density of the irbesartan crystals having the new crystal habit, measured using a Hosokawa machine (180 gravity drops), is about 0.5 kg/m³, whereas that of the crystals of the acicular

form A is about 0.35 kg/m^3 .

The flowability index is calculated by the Carr method (R. Carr: Chemical Engineering, January 18, 1965, page 163-168) and takes into account the results
5 of four experimental values: compressibility, angle of repose, spatula angle and cohesion. This index is about 30 for the crystals of brick habit, whereas it is about 10 for the crystals of acicular habit.

It is found that the resistivity, the minimum
10 inflammation energy, the minimum inflammation temperature, the results of the friction test and gravity of the explosion, measured in a 20-litre sphere, are similar for the two crystal habits of the form A of irbesartan.

15 The fact that the irbesartan crystals of brick habit are of reduced chargeability, i.e. they have a reduced tendency to store electrostatic charges, means that these crystals can be handled more easily and more safely.

20 The 50% increase in the packing density and in the flowability index of the brick habit with respect to the acicular habit represents an improvement which is reflected both in the chemical processability of the product and in their use for their preparation
25 of pharmaceutical forms.

According to the present invention, the irbesartan of brick habit can be prepared using a

process characterized in that a crystalline suspension of irbesartan of acicular habit form A is subjected to at least one sonication episode and at least one temperature oscillation episode.

5 Thus, the sonication episode can be either followed or preceded by the temperature oscillation episode.

 It is also possible to envisage the sonication episode being carried out simultaneously
10 with the temperature oscillation episode. According to the invention, a sonication episode can also be carried out between 2 phases of temperature oscillation.

 Furthermore, the sonication and/or temperature oscillation episodes can be repeated
15 independently of each other.

 Preferably, a sonication episode is preceded by a temperature oscillation episode and more particularly a sonication episode is carried out between 2 temperature oscillation episodes.

20 The term "crystalline suspension" used in the present description refers to an irbesartan suspension prepared according to methods that are known to those skilled in the art. For example, the crystalline suspension can be prepared by growing irbesartan
25 crystals in an organic solvent, for example an alcohol such as isopropanol, to prepare a supersaturated irbesartan solution, and cooling to a temperature at

which the supersaturation is between 0% and 50%. The supersaturated solution is then seeded with 1% to 10% of irbesartan seed crystals of brick habit, the seed crystals originating from a previous batch. However, 5 the seeds may also be generated by repeatedly subjecting the crystalline suspension to temperature oscillation and sonication episodes until crystals of brick habit are obtained. The seeded solution is then cooled to room temperature to form the crystalline 10 suspension. The said crystalline suspension is then used according to the invention.

According to the present invention, a sonication episode consists in subjecting the crystalline suspension to a sonication energy whose 15 frequency is from about 16 kHz to 10 MHz. It appears that the sonication episode limits the growth according to the length of the needles by breaking them and modifies the nature of the crystal surfaces such that the zones capable of accumulating the electrostatic 20 charges are reduced. Sonication methods may be used either batchwise or semi-continuously or continuously.

For the batchwise sonication, an ultrasound probe is inserted into the crystalline suspension placed in a crystallizer.

25 The sonication episode can also be carried out continuously or semi-continuously by pumping the crystalline irbesartan suspension through a sonication

cell at a flow rate of from about 10 litres/min/KW to 20 litres/min/KW; with a pressure of from 0 psig to 100 psig; with an energy of about from 10 000 joules/litre to 30 000 joules/litre and at a frequency of about from 16 kHz to 10 MHz. Preferably, the flow rate is between 16 litres/min/KW and 18 litres/min/KW; the pressure is between 0 psig and 20 psig; the energy is between 16 000 and 25 000 joules/litre and the frequency is about 20 kHz.

10 The above sonication parameters such as the flow rate, the pressure and the frequency vary as a function of the expected result in terms of ratio between the length and the width of the crystals prepared.

15 The temperature oscillation episode comprises a heating phase and a cooling phase. According to the invention, it comprises at least one heating phase and at least one cooling phase in any order. It is preferable for a heating phase to be combined with a cooling phase, and even for the said heating phase to precede the said cooling phase. It is probable that the temperature oscillation contributes towards controlling the correct distribution of the size of the particles; in particular, it tends to dissolve the finer particles and to make the coarser particles grow.

25

 The temperature oscillation is carried out by heating and cooling a crystalline suspension to

predetermined temperatures. The heating phase is performed by heating up to about 20°C to 100°C. Preferably, the heating phase is carried out at a temperature such that about 15% to 25% is dissolved in 60 minutes, more particularly about 20% of the crystals are dissolved in 60 minutes. The cooling phase of the temperature oscillation episode is generally carried out between 100°C and -20°C. Preferably, the cooling phase is carried out at a temperature of between -5°C and 20°C for about 0 to 60 minutes; more particularly between 0 and 5°C for about 0 to 60 minutes.

It should be noted that the temperature selected for the cooling phase of the temperature oscillation episode is less than the temperature selected for the corresponding heating phase. The heating and cooling phases can be repeated independently, as many times as necessary, and the specific parameters may be modified to obtain the desired product.

For example, it is possible to extend the heating phase and shorten the cooling phase to generate shorter crystals or alternatively it is possible to shorten the heating phase and extend the cooling phase to generate larger crystals. The number of heating and cooling phases also depends on the desired result. In general, if the number of heating and cooling phases increases, the appearance of the crystals improves and

the ratio between the length and the width tends towards 1:1.

Controlling the sonication and temperature oscillation parameters makes it possible to control the
5 size distribution of the particles and the ratio between the length and the width of the final crystals.

The process described above for modifying the crystal habit of irbesartan using sonication presents difficulties in industrial implementation.
10 Specifically, the efficacy of the ultrasound emitter decreases beyond a few centimetres from the said emitter; furthermore, when working continuously, this efficiency decreases if the speed of passage of the crystalline suspension treated increases.

15 Also, to treat large volumes, the application time is very long. Moreover, high-power ultrasound causes premature wear of the metals and welds of the apparatus used.

Another process for modifying the crystal
20 habit of the irbesartan form A uses wet grinding, i.e. the mechanical shearing of the crystals of acicular habit to convert them into crystals of brick habit. This process has the advantage of being readily applicable to the treatment of industrial amounts of
25 product.

Thus, according to another of its aspects, the present invention relates to a process for

preparing irbesartan of brick habit, characterized in that it contains the steps consisting in:

- a) preparing a solution of irbesartan form A in an alcohol, under concentration and temperature conditions which allow the total solubility of the irbesartan;
- b) cooling the said solution to a temperature selected as a function of the concentration of the solution, such that the solution is in the metastable zone;
- c) seeding with irbesartan crystals of brick habit;
- d) cooling the irbesartan solution to a temperature of between about 20°C and 5°C;
- e) subjecting the crystalline suspension thus formed to a mechanical shearing using a shearing machine;
- f) heating the crystalline suspension to a temperature of between about 40°C and 60°C to dissolve the fine particles;
- g) cooling the crystalline suspension to a temperature of between about 20°C and 5°C;
- h) filtering off the crystals of brick habit thus formed.

According to the present invention, a solution of irbesartan in alcohol, for example ethanol or, preferably, isopropanol, is used.

Figure 1 indicates, for a solution of irbesartan form A in isopropanol, the conditions for total solubility, as a function of the concentration in g/litre and of the temperature in °C. It also indicates
5 the limits of the metastable zone for a solution containing 25 g/litre to 70 g/litre of irbesartan.

Thus, for a solution of irbesartan in isopropanol containing about 50 g/litre to 70 g/litre, the seeding temperature ranges from 45°C to 80°C in
10 order for the solution to remain in the metastable zone.

The irbesartan solution can be seeded with irbesartan crystals of brick habit at any point in the cooling of the solution, when this solution is in the
15 metastable zone. The seeding temperature is between 25°C and 80°C, depending on the concentration of the solution. The proportion of seed crystals incorporated may be between 1% and 25%, preferably between 10% and 20%. After seeding, the temperature can be kept
20 constant for a period of between a few minutes and 2 hours, preferably for half an hour to one hour.

In steps b) and d), the cooling is advantageously carried out at a uniform cooling rate of about 5°C to 20°C per hour, preferably in the region of
25 10°C per hour.

In step e), the mechanical shearing is preferably carried out with a machine having a spin

speed of about 10 000 to 15 000 rpm.

Machines having such characteristics are, for example, of the Turrax® type, sold by IKA-Werke (Germany). Some of these machines are suitable for
5 treating industrial amounts ranging up to the point of allowing a flow rate of 100 m³/hour. For the process according to the invention and at an industrial stage, a flow rate of between about 500 litres/hour and 4 m³/hour is preferred, in a 2 m³ reactor.

10 The mechanical shearing in step e) can be carried out either by placing the shearing machine in the reactor containing the crystalline suspension, or by passing the crystalline suspension continuously into the shearing machine. In this case, the flow rate of
15 the machine is adjusted as a function of the ratio between the length and the width which is desired for the crystals of brick habit formed.

Optionally, in order to improve the yield of crystals of brick habit, steps e), f) and g) can be
20 repeated before filtering off the crystals of brick habit formed and drying them.

A subject of the present invention is also pharmaceutical compositions containing, as active principle, irbesartan of brick habit, i.e. irbesartan
25 of form A, having a novel crystal habit. These pharmaceutical compositions may be prepared according to the description of patent application EP 747 050.

The formulations prepared with the brick habit can contain up to about 80% by weight of irbesartan or about 85% by weight of irbesartan combined with a diuretic agent, for example hydrochlorothiazide. These formulations may be prepared industrially, for example in the form of tablets or gel capsules, according to known processes, for example by wet granulation, dry granulation or direct tableting.

By tableting, tablets of uniform weight are obtained continuously, these tablets having physical properties that are suitable for industrial development.

EXAMPLE 1

A Preparation of irbesartan form A.

Irbesartan is prepared according to the procedure disclosed in European patent EP 454 511.

1) 2-n-butyl-4-spirocyclopentane-2-imidazoline-5-one

Ethyl amino-1-cyclopentanecarboxylate is prepared according to Adkins and Billica (J. Amer. Chem. Soc., 1948 70, 3121).

Ethyl valerimide is prepared according to Mac Elvain (J. Amer. Chem. Soc., 1942, 64, 1825-1827) and is then released from its hydrochloride by the action of potassium carbonate and extraction with methylene chloride.

Ethyl amino-1-cyclopentanecarboxylate

(1.57 g) and ethyl valerimide (1.56 g) are dissolved in 12 ml of xylene containing 6 drops of acetic acid. After refluxing for six and a half hours, the reaction medium is concentrated under vacuum and the residue is then chromatographed on silica gel, eluting with a chloroform/methanol/acetic acid mixture (94/4/2; v/v/v). The fraction containing the expected product is evaporated several times in the presence of xylene and then of benzene to remove the acetic acid. 1.91 g of product are obtained in the form of a thick oil.

IR (CHCl_3): 1720 cm^{-1} : C = O; 1635 cm^{-1} : C = N.

Comment: the fact that no band is observed between 1500 and 1600 cm^{-1} indicates that, in the chloroform solution, the product is an imidazolin-5-one.

NMR spectrum: 0.92 ppm : t : 3H : CH_3 (nBu); 1.35 ppm : sext : 2H : CH_3CH_2 -.

1.50 - 1.93 ppm : m : 10H : CH_3 - CH_2 - CH_2 and cyclopentane; 2.33 ppm : t : 2H : CH_3 - CH_2 - CH_2 - CH_2 -; 10.7 ppm : m : NH .

Mass spectrum: MH^+ : 195.

The 2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one prepared in step A can also be obtained according to another procedure described below, using cyclopentanone as starting material.

i) 1-aminocyclopentanenitrile

This step is carried out according to

A. Strecker (Org. Synth., 1955, 3).

1.97 g of sodium cyanide are dissolved in 3.9 ml of water in a round-bottomed flask and a solution containing 2.33 g of ammonium chloride in 5.9 ml of water and 3.5 ml of 20% aqueous ammonia is added, and 3 g of cyclopentanone in 3.8 ml of methanol are finally added to the flask. After stirring for 1 and a half hours, the mixture is maintained at 60°C for 45 minutes and heating is then stopped, stirring is continued for 45 minutes and the mixture is then cooled to 25°C. It is extracted several times with methylene chloride. The extracts are dried over sodium sulfate, filtered and concentrated under vacuum. 4 g of the expected product are obtained in oily form.

The 1-aminocyclopentanenitrile obtained is dissolved in 300 ml of acetone and a solution of 2.25 g of oxalic acid dihydrate in 200 ml of acetone is added, with stirring. The precipitate formed is spin-filtered, washed with acetone and then dried.

m = 4.71 g.
m.p. = 220°C.

This compound is 1-aminocyclopentanenitrile hemioxalate.

ii) 1-aminocyclopentaneacetamide.

This step is carried out according to J. Zabicky, (The Chemistry of Amides, Intersciences, New York, 1970, 119).

5.1 g of the oxalate obtained in the preceding step are treated with 7.65 ml of concentrated sulfuric acid ($d = 1.84$) for 45 minutes with stirring. An evolution of gas is observed and the temperature
5 increases to 100°C. The mixture is cooled to about 35°C and is poured into an ice/concentrated aqueous ammonia mixture (10 g/2.8 ml). The suspension formed is extracted 6 times in succession with chloroform containing 5% methanol. 3 ml of aqueous ammonia
10 ($d = 0.92$) is added to the aqueous phase and extraction is repeated with chloroform containing methanol (1/0.5; v/v). The combined organic phases are dried over sodium sulfate, filtered and concentrated. The expected product is obtained in the form of a white solid.

15 $m = 3.79 \text{ g}$
 $m.p. = 95^\circ\text{C}.$

The results of the analysis and the IR spectrum confirm the structure.

iii) 2-n-butyl-4-spirocyclopentane-2-
20 imidazolin-5-one.

This step is performed according to H. Takenaka et al., *Heterocycles*, 1989, 29, (6), 1185-89.

3 g of the compound prepared in the preceding
25 step are placed in 70 ml of anhydrous THF and 3.3 ml of triethylamine, and 3 ml of valeryl chloride in 10 ml of anhydrous THF are added with stirring. A white

suspension forms. The intermediate compound formed, but not isolated, is (N-valeryl)-1-aminocyclopentanecarboxamide. 6 g of potassium hydroxide pellets, 7 ml of water and 16 ml of methanol are added. The mixture is refluxed for 2 and a half hours, followed by addition of 9 g of ammonium chloride. After stirring this mixture for 15 minutes, it is concentrated under vacuum. The residue obtained is taken up in 40 ml of water and extracted with 10 ml of ethyl acetate and then with twice 5 ml of ethyl acetate. The combined organic phases are dried over sodium sulfate and filtered. The filtrate is concentrated to dryness. 4.85 g of the expected product are obtained. The NMR spectrum is similar to that described above. The hydrochloride of this compound can be prepared by adding concentrated hydrochloric acid. The hydrochloride melts at 240°C with sublimation.

2) 1-[(2'-Cyanobiphenyl-4-yl)methyl]-2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one.

A mixture containing 250 mg of sodium hydride (as an 80% dispersion in mineral oil) and 5 ml of DMF is prepared under a nitrogen atmosphere, and a solution containing 0.97 g of 2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one in 10 ml of DMF is added dropwise. The mixture is stirred for 30 minutes at room temperature, followed by addition of a solution of 1.5 g of 4-bromomethyl-2-cyanobiphenyl in 10 ml of DMF. After

stirring for 1 hour at room temperature, the DMF is evaporated off under reduced pressure and the residue is then taken up in ethyl acetate and the organic phase is washed with water and then dried over sodium sulfate, filtered and evaporated. The residue is chromatographed on silica gel, eluting with a DCM/ethyl acetate mixture (9/1; v/v). 1.68 g of the expected product are recovered. m.p. = 92-93°C.

3) 2-n-Butyl-4-spirocyclopentane-1-[2'-(triphenylmethylnitrazol-5-yl)biphenyl-4-ylmethyl]-2-imidazolin-5-one.

1.56 g of the above product, 2.6 g of tributyltin azide and 30 ml of xylene are refluxed for 66 hours. The xylene is then evaporated off and the residue is dissolved in 20 ml of DCM and 5 ml of THF, adding 0.8 ml of 10N sodium hydroxide and, after stirring for 30 minutes, 2.5 g of trityl chloride, and the mixture is left stirring for 26 hours. After evaporation of the solvents, the residue is taken up in ethyl acetate and washed with water, with a 3% potassium hydrogen sulfate solution and with water. The resulting solution is dried and evaporated. The residue is chromatographed on alumina, eluting with a hexane/ethyl acetate (9/1:v/v) mixture. 1.97 g of the expected product are obtained. m.p. = 150-152°C.

4) 2-n-Butyl-4-spirocyclopentane-1-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-

one.

1.96 g of the product prepared in the above step are dissolved in 10 ml of methanol and 10 ml of THF. After cooling of the reaction medium to 5°C,
 5 1.5 ml of 4N hydrochloric acid are added and the mixture is stirred for 3 hours at room temperature and for 1 hour at 30°C. After evaporation of the solvents, the residue is taken up in water and brought to pH 12 by addition of 10N sodium hydroxide. The aqueous phase
 10 is extracted with ether, with toluene and again with ether. The aqueous phase is acidified to pH 2 by addition of 1N hydrochloric acid and is then extracted with ethyl acetate, dried over Na₂SO₄ and evaporated. The white solid obtained is dried at 50°C under 0.05 mm
 15 of mercury. 840 mg of the expected product are obtained. m.p. = 180-181°C.

NMR spectrum: 0.75 ppm : t : 3H : CH₃ (nBu);
 1.10 ppm : sext : 2H : CH₃-CH₂-; 1.20 ppm :
 quint : 2H : CH₃-CH₂-CH₂-; 1.5-2 ppm : m : 8H
 20 : -C₅H₈; 2.2 ppm : t : 2H : CH₃-CH₂-CH₂;
 4.6 ppm : s : 2H : CH₂-C₆H₄-; 7 ppm : s : 4H :
 CH₂-C₆H₄-; 7.35-7.7 ppm : m : 4H : H_{3',4',5',6'}
 aromatic.

The N.O.E. study confirms the position of the
 25 5-one substitution on the imidazole.

The crystals formed can be characterized by their X-ray diffraction spectrum (Table 1) and

correspond to irbesartan form A.

d	I/I ₀
11.22	100.00
7.90	12.02
7.52	13.79
7.23	18.60
6.27	20.14
6.09	6.47
5.86	7.42
5.60	98.76
5.41	19.45
5.05	24.67
4.97	20.36
4.91	12.92
4.80	27.33
4.61	15.90
4.49	14.73
4.36	9.86
4.17	62.84
4.07	15.39
3.97	30.34
3.88	14.32
3.83	13.56
3.75	37.28
3.53	26.48
3.46	12.42

3.40	27.88
3.27	11.03
3.18	10.42
3.15	7.28
3.12	6.11
3.05	15.50
3.01	9.49
2.81	7.11
2.78	9.40

The crystals thus obtained can be recrystallized in the following way.

15 ml of isopropanol are added to 840 mg of the product obtained and the mixture is heated until dissolution is complete. The solution is cooled to room temperature and the crystals formed are then filtered off, washed with water and dried. 805 mg of irbesartan form A are obtained.

10 B Preparation of the seed crystals.

The crystals subsequently used as seeds are prepared according to the following procedure.

Cycle I

15 A three-necked round-bottomed flask fitted with a mechanical stirrer is loaded with 200 ml of isopropyl alcohol and 9.40 g of the compound obtained in step A. The crystalline suspension is heated at 77.0°C, with stirring (about 100 rpm), until

dissolution is complete. The solution is cooled to 73.0°C and a further 0.09 mg of the compound from step A is added to initiate the crystallization. The crystalline suspension is cooled to 20.0°C over 20 minutes. The suspension is subjected to sonication for 600 seconds at a power of 10-15 watts, using a 0.63 cm O.D. sonication probe.

Cycle II.

The crystalline suspension is heated to 74.0°C, which dissolves about 93% of the crystals, leaving only the largest crystals for the next crystallization.

The mixture is cooled to 20.0°C over 180 minutes according to the cubic temperature decrease described below:

Time, minutes	Temperature, °C
0	74.0
30	73.8
60	72.0
90	67.3
120	58.0
150	42.8
180	20.0

When the temperature of 20.0°C is reached, the reaction medium is subjected to sonication for 600

seconds at a power of 10-15 watts.

Cycle III.

The crystalline suspension is heated to 74.0°C. As in cycle II, it is cooled to 20.0°C over 180 minutes, according to the cubic temperature decrease described above. When the temperature of 20.0°C is reached, the crystalline suspension is subjected to sonication for 600 seconds at a power of 10 to 15 watts.

10 Cycle IV.

The crystalline suspension is heated to 74.0°C. As in cycle II, it is cooled to 20.0°C over 180 minutes, according to the cubic temperature decrease described above. When the temperature of 20.0°C is reached, the crystalline suspension is subjected to sonication for 600 seconds at a power of 10 to 15 watts.

Cycle V.

The crystalline suspension is heated to 74.0°C. As in cycle II, it is cooled to 20.0°C over 180 minutes, according to the cubic temperature decrease described above. When the temperature of 20.0°C is reached, the crystalline suspension is subjected to sonication for 600 seconds at a power of 10 to 15 watts.

Cycle VI.

The crystalline suspension is heated to

74.0°C. As in cycle II, it is cooled to 20.0°C over 180 minutes, according to the cubic temperature decrease described above. The crystalline suspension is cooled to 5.0°C and the product is filtered off on a Buchner
5 funnel and dried under vacuum at 70°C overnight to give the seed crystals.

C Crystallization procedure

515 g of the compound from step A are mixed with 10.95 litres of isopropanol to form the
10 crystalline suspension. This is heated to 80°C to dissolve all of the solid. The crystalline suspension is then cooled to 20°C according to the cubic temperature decrease described above, over 4 hours and with addition at 73°C of 5.13 g of seed crystals,
15 obtained in step B. A 1.27 cm O.D. sonication probe is introduced for 10 minutes at a power of 125 W. The solution is heated again to 73°C to dissolve the small crystals and is then cooled to 20°C over 4 hours according to the cubic temperature decrease described
20 above.

The solution is then subjected to sonication for 10 minutes at a power of 125 W. The solution is heated again to 73°C to dissolve the small crystals. The solution is cooled to 2°C, using the cubic
25 temperature decrease described above, over 6 hours and the solution is then maintained at 2°C for 1 hour. The reaction medium is filtered to form a wet filtrate.

This is dried at 50°C under vacuum overnight. 513.4 g of the dry product are obtained, having a width:length ratio of 1:2 to 1:5.

EXAMPLE 2

- 5 A) Preparation of the solution of irbesartan of form A.

The process is performed according to the procedure described in Example 1, step A. 116 kg of irbesartan and 1585 l of isopropanol are loaded into a
10 2000 l reactor and the mixture is then refluxed for 30 minutes to obtain total dissolution. The solution is hot-filtered, to remove the insoluble particles, into another reactor, passing via a cartridge with a 0.6 µm cut-off threshold. The filtered solution is refluxed
15 again to dissolve any seed crystals present, and is then cooled to 80°C with stirring at about 50 rpm.

- B) Preparation of the seed crystals.

The seed crystals are obtained in the laboratory in successive steps of heating and cooling
20 of a solution of irbesartan form A in isopropanol, the solution undergoing a passage through the shearing machine (Turrax®) after each cooling.

- C) Crystallization procedure

a) A suspension of seed crystals containing
25 17.4 kg in 33 l of isopropanol is prepared and is introduced in a single portion into the solution prepared in step A and maintained at 80°C for 1 hour.

The temperature of the reactor is reduced to 20°C at a uniform cooling rate of 10°C per hour. A population of crystals is obtained whose length is 300 µm to 500 µm and whose width is 20 µm to 50 µm at the end of
 5 crystallization, i.e. a ratio of 25:1 to 6:1.

b) The crystalline suspension is treated for 35 minutes (flow rate of 4 m³/hour) in a Turrax® shearing machine, referenced IKA/DISPAX Reactor DRS 2/10, at a spin speed of 12 000 rpm. Crystals are
 10 obtained having a length of 40 µm to 110 µm and a width of 5 µm to 40 µm, i.e. a ratio of 8:1 to 1:1. Many fine particles are also present.

c) The temperature of the reactor is raised to 50°C and this temperature is maintained for 1 hour
 15 to dissolve the fine particles.

d) The temperature of the reactor is reduced to 5°C at a uniform cooling rate of 10°C per hour and is then maintained at this temperature for one hour.

e) By filtration, a population of crystals of
 20 brick habit is obtained (average length 30 µm, average width 5 µm, ratio 6:1). After drying, 121 kg of crystals of brick habit with an isopropanol content of less than 1000 ppm are obtained.

EXAMPLE 3 Tablet: percentage formulation

25	Irbesartan of brick habit	70
	Microcrystalline cellulose	24.75
	Sodium croscarmellose	3.75

Hydrated colloidal silica	0.75
Magnesium stearate	0.75

EXAMPLE 4 Tablet: percentage formulation

	Irbesartan of brick habit	70
5	Microcrystalline cellulose	12.375
	Sodium croscarmellose	3.75
	Polyethylene glycol	12.375
	Hydrated colloidal silica	0.75
	Magnesium stearate	0.75

10 EXAMPLE 5 Tablet

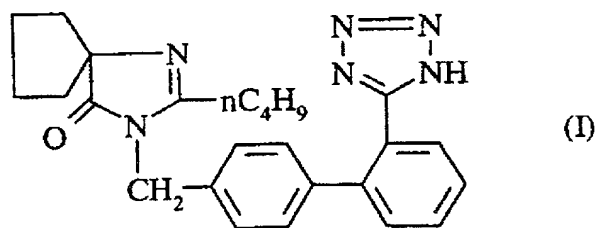
	Irbesartan of brick habit	75 mg
	Hydrochlorothiazide	12.50 mg
	Microcrystalline cellulose	7.75 mg
	Sodium croscarmellose	3.25 mg
15	Hydrated colloidal silica	0.75 mg
	Magnesium stearate	0.75 mg
	Per tablet	

EXAMPLE 6 Tablet

	Irbesartan of brick habit	150 mg
20	Hydrochlorothiazide	12.50 mg
	Microcrystalline cellulose	15.50 mg
	Sodium croscarmellose	6.50 mg
	Hydrated colloidal silica	1.50 mg
	Magnesium stearate	1.50 mg
25	Per tablet.	

CLAIMS

1. Crystalline compound of formula:



having a crystal habitus such that the ratio between the length and the width of the crystals is between 1:1 and 10:1.

2. Crystalline compound according to Claim
5 1, in which the ratio between the length and the width of the crystals is between 1:1 and 5:1.

3. Novel crystalline form of irbesartan of form A, characterized in that the ratio between the length and the width of the crystals is between 1:1 and
10 5:1.

4. Process for preparing a compound according to any one of Claims 1 to 3, characterized in that a crystalline suspension of a compound of formula (I) is subjected to at least one sonication episode and
15 at least one temperature oscillation episode.

5. Process for preparing a compound according to any one of Claims 1 to 3, characterized in that a crystalline suspension of irbesartan of acicular habit form A is subjected to at least one sonication
20 episode and at least one temperature oscillation episode.

6. Process according to either of Claims 4 and 5, in which the temperature oscillation episode comprises a heating phase and a corresponding cooling
25 phase.

7. Process according to Claim 6, in which the heating phase precedes the cooling phase.

8. Process according to Claim 7, in which the sonication episode is followed by a temperature oscillation episode.

9. Process according to either of Claims 4 and 5, in which the sonication episode is preceded by a temperature oscillation episode.

10. Process according to either of Claims 4 and 5, in which the sonication episode is carried out simultaneously with the temperature oscillation episode.

11. Process according to either of Claims 4 and 5, in which a sonication episode is carried out between 2 temperature oscillation episodes.

12. Process according to either of Claims 4 and 5, in which the sonication and/or temperature oscillation episodes are repeated independently.

13. Process according to either of Claims 4 and 5, in which the sonication is carried out in batches, semi-continuously or continuously.

14. Process according to Claim 7, in which the heating phase of the temperature oscillation episode is carried out at a temperature of between about 20°C and 100°C.

15. Process according to Claim 7, in which the heating phase of the temperature oscillation episode is carried out at a temperature such that about 15% to 25% of the crystals are dissolved in about 60

minutes.

16. Process according to Claim 7, in which the cooling phase of the temperature oscillation episode is carried out at a temperature of between
5 about 100°C and -20°C.

17. Process according to Claim 7, in which the cooling phase of the temperature oscillation episode is carried out at a temperature of between about -5°C and 20°C.

10 18. Process according to Claim 7, in which the temperature selected for the cooling phase of the temperature oscillation episode is less than the temperature selected for the corresponding heating phase of the temperature oscillation episode.

15 19. Process according to Claim 7, in which the crystalline suspension is seeded with irbesartan crystals whose ratio between the length and the width is between 1:1 and 10:1.

20 20. Process for preparing a compound according to any one of Claims 1 to 3, characterized in that it contains the steps consisting in:

a) preparing a solution of irbesartan acicular habit form A in an alcohol, under concentration and temperature conditions which allow
25 the total solubility of the irbesartan;

b) cooling the said solution to a temperature selected as a function of the concentration of the

solution, such that the solution is in the metastable zone;

c) seeding with irbesartan crystals of brick habit;

5 d) cooling the irbesartan solution to a temperature of between about 20°C and 5°C;

e) subjecting the crystalline suspension thus formed to a mechanical shearing using a shearing machine;

10 f) heating the crystalline suspension to a temperature of between about 40°C and 60°C to dissolve the fine particles;

g) cooling the crystalline suspension to a temperature of between about 20°C and 5°C;

15 h) filtering off the crystals of brick habit thus formed.

21. Process according to Claim 20, in which, in step a), the irbesartan is dissolved in isopropanol.

22. Process according to Claim 20, in which,
20 in step b), a solution containing 50 g/litre to 70 g/litre of irbesartan in isopropanol is cooled to a temperature ranging between 60°C and 80°C.

23. Process according to Claim 20, in which, in step c), the solution is seeded with irbesartan
25 crystals whose ratio between the length and the width is between 1:1 and 10:1.

24. Process according to Claim 23, in which

the seeded solution is maintained at a temperature of between 80°C and 22°C for a few minutes to about 2 hours, before being cooled.

25. Process according to Claim 21, in which,
5 in steps b) and d), the rate of cooling is from about 5°C to 20°C per hour.

26. Process according to Claim 20, in which,
in step e), the mechanical shearing is carried out by a machine having a spin speed of about from 10 000 rpm to
10 15 000 rpm.

27. Process according to Claim 26, in which
the mechanical shearing in step e) is carried out
either by placing the shearing machine directly in the reactor or by passing the crystalline suspension into
15 the shearing machine.

28. Pharmaceutical composition containing a compound according to any one of Claims 1 to 3 and pharmaceutically acceptable excipients.

29. Pharmaceutical composition according to
20 Claim 28, containing a diuretic agent combined with a compound according to any one of Claims 1 to 3.

30. Pharmaceutical composition according to Claim 29, in which the diuretic agent is hydrochlorothiazide.

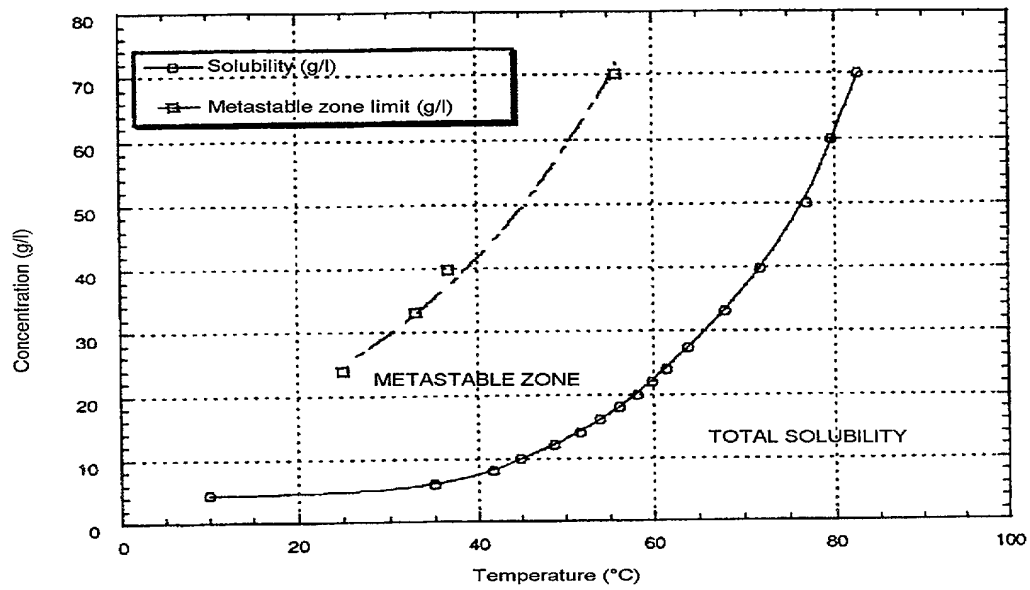


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<p>(21) Numéro de la demande internationale: PCT/FR99/01372</p> <p>(22) Date de dépôt international: 10 juin 1999 (10.06.99)</p> <p>(30) Données relatives à la priorité: 98/08037 24 juin 1998 (24.06.98) FR</p> <p>(71) Déposant (pour tous les Etats désignés sauf US): SANOFI-SYNTHELABO [FR/FR]; 174, avenue de France, F-75013 Paris (FR).</p> <p>(72) Inventeurs; et (75) Inventeurs/Déposants (US seulement): FRANC, Bruno [FR/FR]; 6, rue de l'Oratoire, F-30650 Saze (FR). HOFF, Christian [FR/FR]; Mazet de l'Escoraille, F-30126 Saint Laurent des Arbres (FR). KIANG, Sam [US/US]; 16 Highland Avenue, Madison, NJ 07940 (US). LINDRUD, Mark, D. [US/US]; 25 Ridgedale Avenue, Madison, NJ 07940 (US). MONNIER, Olivier [FR/FR]; 20, route de Poussan, F-34560 Villeveyrac (FR). WEI, Chenkou [US/US]; 44 Windsor Drive, Princeton Junction, NJ 08688 (US).</p> <p>(74) Représentant commun: SANOFI-SYNTHELABO; Dépt. Brevets, 174, avenue de France, F-75013 Paris (FR).</p>		<p>(81) Etats désignés: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, brevet ARIPO (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), brevet eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet européen (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), brevet OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Publiée <i>Avec rapport de recherche internationale.</i></p>
<p>(54) Title: <u>NOVEL FORM OF IRBESARTAN, METHODS FOR OBTAINING SAID FORM AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME</u></p>		
<p>(54) Titre: NOUVELLE FORME DE L'IRBESARTAN, PROCEDES POUR OBTENIR LADITE FORME ET COMPOSITIONS PHARMACEUTIQUES EN CONTENANT</p>		
<p>(57) Abstract</p>		
<p>The invention concerns irbesartan form A having a modified crystalline habit such that length/width ratio ranges between 1:1 and 10:1, preferably between 1:1 and 5:1 and a method for preparing said crystalline habit. The method is characterised in that it consists in either subjecting a crystalline suspension of irbesartan form A having acicular habit to at least a temperature oscillating step, or in subjecting a crystalline suspension of irbesartan form A having acicular habit to a mechanical shearing. The invention also concerns a pharmaceutical composition containing said irbesartan crystalline habit.</p>		
<p>(57) Abrégé</p>		
<p>Irbesartan forme A ayant un habitus cristallin modifié de sorte que le rapport entre la longueur et la largeur des cristaux soit compris entre 1:1 et 10:1, préférentiellement entre 1:1 et 5:1 et un procédé pour la préparation de cet habitus cristallin caractérisé en ce que, soit on soumet une suspension cristalline d'irbesartan forme A d'habitus aiguille à au moins un épisode d'oscillation de température, soit on soumet une suspension cristalline d'irbesartan forme A d'habitus aiguille à un cisaillement mécanique. Composition pharmaceutique contenant ledit habitus cristallin de l'irbesartan.</p>		

Figure 1

SOLUBILITY AND METASTABLE ZONE LIMIT OF
IRBESARTAN FORM A IN ISOPROPANOL



1018

**DECLARATION AND POWER OF ATTORNEY FOR
UNITED STATES PATENT APPLICATION**

 X Original Supplemental Substitute

As a below-named inventor, I hereby declare that:

My residence, citizenship and post office address are given below under my name.

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NOVEL FORM OF IRBESARTAN METHODS FOR OBTAINING SAID FORM AND
PHARMACEUTICAL COMPOSITIONS CONTAINING SAME.

the specification of which

 is attached hereto.

 was filed on as United States
Application Serial No.
and was amended on (if applicable).

 X was filed on 10 June 1999 as PCT International
Application No. PCT/FR99/01372
and was amended under PCT Article 19 on (if applicable).

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge my duty to disclose information of which I am aware which is material to the examination of this application in accordance with Section 1.56 of Title 37 of the Code of Federal Regulations.

I hereby claim foreign priority benefit under Section 119 (a) - (d) of Title 35 of the United States Code of any foreign application(s) for patent or inventor's certificate or of any PCT application(s) designating at least one country other than the United States identified below and also identify below any foreign application(s) for patent or inventor's certificate or any PCT application(s) designating at least one country other than the United States filed by me on the same subject matter and having a filing date before that of the application(s) from which priority is claimed:

<u>Country</u>	<u>Number</u>	<u>Filing Date</u>	<u>Priority Claimed</u>	
			<u>Yes</u>	<u>No</u>
France	98 08037	24 June 1998	X	

I hereby claim benefit under Section 120 of Title 35 of the United States Code of any United States application(s) or PCT application(s) designating the United States identified below and, insofar as the subject matter of each of the claims of this application is not disclosed in said prior application(s) in the manner provided by the first paragraph of Section 112 of Title 35 of the United States Code, I acknowledge my duty to disclose material information of which I am aware as defined in Section 1.56 of Title 37 of the Code of Federal Regulations which occurred between the filing date of the prior application(s) and the national or PCT filing date of this application:

<u>Application Serial No.</u>	<u>Filing Date</u>	<u>Status</u>
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I hereby appoint Michael D. Alexander, Reg. No. 36,080; and Paul E. Dupont, Reg. No. 27,438, or any of them my attorneys or agents with full power of substitution and revocation to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

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I hereby declare that all statements made herein and in the above-identified specification of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first joint inventor

FRANC Bruno

Inventor's signature

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